



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF :
Ikuro MARUYAMA, ET AL. : EXAMINER: EPPS FORD, JANET L
SERIAL NO.: 10/577,447 :
FILED: April 27, 2006 : GROUP ART UNIT: 1633
FOR: ANTITUMOR MEDICINE :

DECLARATION UNDER 37 C.F.R. 1,132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

I, Kazuhiro Abeyama, am one of the inventors of the present invention. I am a medical doctor, a doctor of medicine and associate professor teaching clinical preventive medicine at the Postgraduate Department of Medical Dentistry Advanced Study of Kagoshima University of Japan.

I swear the following as for the anticancer effect of known antioxidants and that of APP used in the present application to the best of my knowledge.

The main mechanisms of the anticancer effect of the known antioxidants such as vitamin E are assumed to be the function of: (1) reducing DNA mutagenesis caused by oxidative stress-induced DNA damage, (2) reducing productions of proinflammatory cytokine and growth factors which act as potent inducers of additional oxidant stress and contribute to cancer progression, (3) suppressing "growth signaling" in the cell, for example, the inhibition of enzymatic activities of tyrosine kinase, protein kinase C and MAPK and its resultant suppression of transcription factors NF-kB and AP-1. However, an ordinary "antioxidant having an anticancer effect" has no significant cell killing effect for cancer cells directly and rather serves to protect cells. The delay of G1 period of the cell cycle (G1 arrest) is suggested to involve in the mechanism of the antioxidant effect of cytoprotection demonstrating growth inhibition.

Meanwhile, although the functions (above functions (1) to (3)) of the so-called antioxidant are also expected as the mechanism of the anticancer effect of APP, unlike the ordinary "antioxidant having an anticancer effect", APP has a cell-killing effect for cancer cells directly, that is, the function of

apoptosis induction in cancer cells. Characteristically, the pharmacological function is dominant in highly proliferating cells. Further, in the anticancer effect, APP has the "function of induction of "delaying the S period" by cancer cells without showing "G1 arrest", suggesting the direct inhibitory effect of the agent on DNA synthesis. The pharmacological function is particular in APP, not seen in ordinary known antioxidants, which classifies APP not only as a "preventative (e.g., common antioxidants) but also as therapeutic agent (e.g., cisplatin, 5-FU, adriamycin, etc.) against cancer in the category of anticancer agents. The "anticancer effect of APP" is thus considered to be completely different from that of known antioxidants.

Concerning the issue of advantage of APP, the agent can also be expected to have cytoprotective effect in normal cells without highly proliferative character through quenching oxidative stress. In the context of adverse effect of commonly used anticancer agents, for example, nephrotoxic potential in the case of cisplatin and myocardial toxicity in the case of adriamycin are developed through the mechanism based on oxidative stress and its resultant inflammation outbreak. By using APP in combination with any one of these anticancer agents, APP is thus expected to attenuate the adverse effects of common anticancer agents that generate oxidative stress and synergistically increase the cancer effects.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Further declarant saith not.

Kapil Chhaya
Signature

5/10/2008
Date